IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GENENTECH, INC. and INTERMUNE, INC., Plaintiffs, v. SANDOZ, INC. and LEK PHARMACEUTICALS D.D., Defendants.	Civil Action No. 19-0078-RGA

TRIAL OPINION

Jack B. Blumenfeld, Karen Jacobs, Cameron P. Clark, MORRIS NICHOLS ARSHT & TUNNELL LLP, Wilmington, DE; Mark E. Waddell, Warren K. MacRae, Ryan Hagglund, Kathleen Gersh, LOEB & LOEB LLP, New York, NY; Alexandra Cavazos, Dan Liu, LOEB & LOEB LLP, Los Angeles, CA.

Attorneys for Plaintiffs.

Stephen B. Brauerman, BAYARD, P.A., Wilmington, DE; Emily L. Rapalino, Daryl L. Wiesen, Nicholas K. Mitrokostas, Kathleen A. McGuinness, Tiffany Mahmood, Natasha Daughtrey, GOODWIN PROCTER LLP, Boston, MA.

Attorneys for Defendants.

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ANDREWS, U.S. DISTRICT JUDGE:

Plaintiffs brought this patent infringement action on January 14, 2019, alleging Defendants' submission of Abbreviated New Drug Applications ("ANDAs") seeking approval from the FDA to market a generic version of Plaintiffs' drug Esbriet® (pirfenidone), infringed several of its patents. (D.I. 1). Plaintiffs asserted six patents at the bench trial, which began on November 8, 2021. There were three days of testimony (D.I. 370, 371, 372, hereinafter referred to as "Tr."), closing argument (D.I. 373), and both parties submitted post-trial briefing and proposed findings of fact regarding infringement and invalidity. (D.I. 374, 375, 376, 377, 378, 379, 380, 381, 382, 383). My findings of fact and conclusions of law follow. *See* Fed. R. Civ. P. 52(a).

I. BACKGROUND

This action arises from Defendants ("Sandoz")[1] filing ANDA Nos. 212600 and 212560 seeking to market 267 mg pirfenidone capsules and 267 mg and 801 mg pirfenidone tablets prior to the expiration of Plaintiffs' patents. (D.I. 343-1 ¶¶ 1, 24-33).

Pirfenidone is a drug used to treat idiopathic pulmonary fibrosis ("IPF"). IPF is a chronic, irreversible, and devastating lung disease. (Tr. 49:9-14). The disease is characterized by scarring (fibrosis) of the network of tissue that supports the air sacs of the lungs, resulting in severe difficulty breathing and progressive impairment of a patient's ability to perform everyday activities. (Tr. 49:15- 50:13). There is no cure for IPF and patients living with the disease face an average survival of two to five years. (Tr. 49:11-14, 302:16-17). There are currently two drugs that have been approved by the FDA for the treatment of IPF, pirfenidone and nintedanib. (Tr. 303:10-12). Both drugs have been proven to slow the rate of decline in lung function by about 50% over

[1] Defendants share the same counsel. In Defendants' post-trial briefing, they refer to both Sandoz, Inc. and Lek Pharmaceuticals as "Sandoz/Defendant." (D.I. 376 at iii). I adopt the same nomenclature here.

time. (Tr. 304:1-3). Approximately half of patients "on treatment" for IPF are prescribed pirfenidone and approximately half are prescribed nintedanib. (Tr. 303:13-16). The major differences between the drugs "center on side effects and metabolism." (Tr. 304:4-6).

Side effects associated with pirfenidone include anorexia, nausea, and photosensitive skin rash, while nintedanib has been associated with diarrhea and loose stool. (Tr. 304:6-10). Pirfenidone is primarily metabolized "through the CYP1A2 enzyme pathway" with contributions from other CYP enzymes, whereas nintedanib has a "completely different" metabolic pathway, relying primarily on ester cleavage with only "minor metabolism through the CYP3A4 pathway." (Tr. 304:11-21). Pulmonologists consider a number of factors when deciding which drug to prescribe to their IPF patients, including the patient's preference/tolerance for each drug's dosing schedule and side effects and the patient's insurance coverage, as the medications each "cost about $100,000 a year." (Tr. 305:1-7).

Pirfenidone was first studied as an "investigational new drug" in 1973 by Affiliated Medical Research, Inc. (PTX0234 at 51). Development rights to pirfenidone were subsequently transferred to Marnac. (*Id.*). In 1997, Marnac sold to Shionogi rights to pirfenidone for Japan, South Korea, and Taiwan "for development in fibrotic indications," and in 2002, Marnac sold to InterMune rights to pirfenidone for the rest of the world. (*Id.*). On March 5, 2004, the FDA granted pirfenidone U.S. "orphan drug" status for the treatment of patients with IPF. (*Id.*).

At trial, Plaintiffs asserted various claims of six patents directed toward treatment methods involving pirfenidone: (i) claim 9 of U.S. Patent No. 7,566,729 ("the '729 patent") (JTX0001), (ii) claims 6 and 14 of U.S. Patent No. 7,635,707 ("the '707 patent") (JTX0002), (iii) claims 12 and 28 of U.S. Patent No. 8,592,462 ("the '462 patent") (JTX0003), (iv) claim 19 of U.S. Patent No. 8,609,701 ("the '701 patent") (JTX0004), (v) claim 6 of U.S. Patent No. 7,816,383 ("the '383

patent") (JTX0005), and (vi) claims 3 and 9 of U.S. Patent No. 8,013,002 ("the '002 patent") (JTX0007) (collectively, the "Asserted Patents" and "Asserted Claims").

The '729, '707, '462, and '701 patents ("the Liver Function Test (LFT) patents") are directed toward methods "for administering pirfenidone to a patient that has exhibited abnormal biomarkers of liver function in response to pirfenidone administration." (JTX0001 at 1; JTX0002 at 1; JTX0003 at 1; JTX0004 at 1). The '383 and '002 patents ("the Drug-Drug Interaction (DDI) patents") are directed toward "methods involving avoiding adverse drug interactions with fluvoxamine and pirfenidone or other moderate to strong inhibitors of CYP enzymes." (JTX0005 at 1; JTX0007 at 1).

A. The LFT Patents

Throughout InterMune's development of pirfenidone, potential hepatotoxicity issues presented by the drug were "fairly front and center" in its development plan. (Tr. 81:7-16). InterMune knew Marnac had observed the development of "liver necrosis" in a patient taking pirfenidone and Shionogi had observed one patient who exhibited "very severe liver injury" that met the criteria for "Hy's law"[2] in its Phase II study, in which fewer than one hundred patients were dosed with pirfenidone. (Tr. 64:13-23, 66:2-25, 150:3-18). The FDA also expressed concerns about pirfenidone and potential liver toxicity. (Tr. 65:21-66:9). Following InterMune's "End-of-Phase-2 Meeting" with the FDA in December 2004, the FDA warned InterMune, "Because of the abnormal liver function tests noted in the Shionogi study, you should consider excluding subjects

[2] "Hy's Law" describes the observation that "hepatocellular injury sufficient to impair bilirubin excretion [cause jaundice]" is "ominous." (PTX0149 at 7). The FDA has used Hy's Law to "identify drugs likely to be capable of causing severe liver injury." (*Id.*). The U.S. Department of Health and Human Services warns in its "Guidance for Industry" regarding drug-induced liver injury ("DILI"), "Finding one Hy's Law case in clinical trials is ominous; finding two is highly predictive of a potential for severe DILI." (*Id.* at 8).

[from your pirfenidone clinical trials] with any significant liver disease." (PTX0235 at 1, 30). In response to these concerns, InterMune developed a "liver function test management plan" to find a way to safely allow patients exhibiting signs of abnormal liver function to continue pirfenidone treatment. (Tr. 81:7-25).

InterMune's "liver function test management plan" gave rise to the LFT patents, which relate to "methods for reducing abnormal liver function associated with [pirfenidone] therapy." (JTX0001 at 2; JTX0002 at 2; JTX0003 at 3; JTX0004 at 4). "Abnormal liver function may manifest as abnormalities in levels of biomarkers of liver function, including alanine transaminase ["ALT"], aspartate transaminase ["AST"], bilirubin, and/or alkaline phosphatase, and may be an indicator of drug-induced liver injury." (JTX0001 at 2). Liver function tests are graded in order of severity, with a "Grade 2" being "a severity range where the enzymes are typically two and a half to five times the upper limit of the normal range." (Tr. 85:10-15).

The Asserted Claims of the LFT patents disclose methods for responding to a Grade 2 abnormality in liver function biomarkers (specifically, ALT and AST) in a patient taking pirfenidone to treat IPF by doing one of the following: (1) temporarily reducing the dose of pirfenidone and then returning to the full dose (2400 mg/day or 2403 mg/day),[3] (2) maintaining the full dose of pirfenidone (2400 mg/day or 2403 mg/day), (3) reducing the dose of pirfenidone to 1600 mg/day or 1602 mg/day, (4) discontinuing pirfenidone "for about a week" and then returning to the full dose, (5) discontinuing pirfenidone "for about a week" and then returning to a dose of "at least 1600 mg/day," or (6) reducing the dose of pirfenidone to "at least 1600 mg/day or 1602 mg/day."

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[3] "The exact dose of 2,403 milligrams per day was chosen based on the capsule size, which was 267 milligrams, which was designed to permit thrice daily dosing with a number of capsules that fostered simple dose modifications, if necessary." (Tr. 284:13-17 (Samuels)).

Claim 9 of the '729 patent is a dependent claim of unasserted independent claim 1, disclosing, "The method of claim 1, wherein said one or more biomarkers of liver function comprise alanine transaminase and aspartate transaminase." (JTX0001 at 7). Claim 1 of the '729 patent discloses:

> A method of administering pirfenidone to treat a patient with idiopathic pulmonary fibrosis (IPF), said patient having exhibited a grade 2 abnormality in one or more biomarkers of liver function after pirfenidone administration, comprising
> (a) administering to said patient pirfenidone at doses lower than 2400 mg/day for a time period, followed by
> (b) administering to said patient pirfenidone at doses of 2400 mg/day or 2403 mg/day.

(*Id.*).

Claim 6 of the '707 patent is a dependent claim of unasserted independent claim 1, disclosing, "The method of claim 1, wherein said one or more biomarkers of liver function is selected from the group consisting of alanine transaminase and aspartate transaminase." (JTX0002 at 10). Claim 1 of the '707 patent discloses:

> A method of administering pirfenidone to treat a patient with idiopathic pulmonary fibrosis (IPF), said patient having exhibited a grade 2 abnormality in one or more biomarkers of liver function after pirfenidone administration, comprising
> (a) administering to said patient pirfenidone at doses of 2400 mg/day or 2403 mg/day.

(*Id.*).

Claim 14 of the '707 patent is a dependent claim of unasserted independent claim 7, disclosing, "The method of claim 7, wherein said one or more biomarkers of liver function is selected from the group consisting of alanine transaminase and aspartate transaminase." (*Id.* at 11). Claim 7 of the '707 patent discloses:

> A method of administering pirfenidone to treat a patient with idiopathic pulmonary fibrosis (IPF), said patient having exhibited a grade 2

> abnormality in one or more biomarkers of liver function after pirfenidone administration, comprising (a) administering to said patient pirfenidone at doses of 1600 mg/day or 1602 mg/day.

(*Id.* at 10).

Claim 12 of the '462 patent is a dependent claim of unasserted dependent claim 3, disclosing, "The method of claim 3 further comprising, prior to step (a), discontinuing the first administration of pirfenidone for about a week, or until biomarkers of liver function are within normal limits." (JTX0003 at 12). Claim 3 of the '462 patent is a dependent claim of unasserted independent claim 1, disclosing, "The method of claim 1, wherein step (a) comprises administering to said patient pirfenidone at a dose of about 2400 mg/day or 2403 mg/day." (*Id.* at 11). Claim 1 of the '462 patent discloses:

> A method of administering pirfenidone to treat a patient with idiopathic pulmonary fibrosis (IPF), said patient having exhibited an increase of about 2.5-fold to about 5-fold, compared to the upper limit of normal, in one or both of alanine transaminase and aspartate transaminase after a first pirfenidone administration, comprising providing to said patient a second administration of pirfenidone, comprising (a) administering to said patient pirfenidone at a dose of at least 1600 mg/day.

(*Id.*).

Claim 28 of the '462 patent is a dependent claim of unasserted independent claim 26, disclosing, "The method of claim 26 further comprising, prior to step (a), discontinuing the first administration of pirfenidone for about one week, or until biomarkers of liver function are within normal limits." (*Id.* at 12). Claim 26 of the '462 patent discloses:

> A method of administering pirfenidone to treat a patient with idiopathic pulmonary fibrosis (IPF), said patient having exhibited a Grade 2 abnormality in one or both of alanine transaminase and aspartate transaminase after a first pirfenidone administration, comprising providing to said patient a second administration of pirfenidone, comprising (a) administering to said patient pirfenidone at a dose of at least 1600 mg/day.

(*Id.*).

Claim 19 of the '701 patent is a dependent claim of unasserted independent claim 1, disclosing, "The method of claim 1, wherein the patient suffers from idiopathic pulmonary fibrosis." (JTX0004 at 13). Claim 1 of the '701 patent discloses:

> A method of treating a patient in need of pirfenidone and suffering from a Grade 2 abnormality in a liver function biomarker selected from the group consisting of alanine transaminase (ALT) and aspartate transaminase (AST) and wherein the abnormality occurs after a first pirfenidone administration, comprising providing to said patient a second administration of pirfenidone, comprising (a) administering to said patient at doses of at least 1600 mg/day or 1602 mg/day.

(*Id.* at 12).

B. The DDI Patents

In 2008, InterMune conducted a study to examine the "effect of fluvoxamine as a strong CYP1A2 inhibitor on the [pharmacokinetics] of Pirfenidone." (Tr. 109:9-14). CYP1A2 is a member of the cytochrome P-450 system, which comprises a group of "enzymes that are involved in the metabolism of drugs and, in this case, Pirfenidone." (Tr. 109:15-18). "[T]he metabolism of Pirfenidone is heavily mediated through the CYP1A2 enzyme pathway . . . but there are contributions from other CYP enzymes as well." (Tr. 304:13-16). Normally, when pirfenidone enters a patient's body, it is "metabolized or broken down" by enzymes, such as the CYP1A2 enzyme. (Tr. 329:14-21). CYP inhibitors can interfere with normal drug metabolism by inhibiting the CYP enzymes' ability to metabolize the drug, resulting in "supratherapeutic" levels of un-metabolized drug in the body. (Tr. 329:14-330:6). This can cause "adverse events all throughout the body," especially when the drug is toxic in its unmetabolized form. (*Id.*). Fluvoxamine is well-known as "a strong CYP1A2 inhibitor." (PTX0241 at 3).

Nintedanib, which is metabolized primarily via ester cleavage, is not susceptible to drug-drug interaction with CYP1A2 inhibitors. (Tr. 330:12-17). Pirfenidone, however, is highly susceptible to drug-drug interaction with CYP1A2 inhibitors. (Tr. 329:5-330:3). InterMune first

discovered this in its 2008 study, finding "the blood concentrations of Pirfenidone on average went up six times, sixfold, in patients that were on – in subjects that were on fluvoxamine. So that's a very substantial drug-drug interaction, particularly in the context of Pirfenidone." (Tr. 110:19-23). Because pirfenidone "is a drug with a lot of toxicities," InterMune understood that "to have a situation where the concentrations in the blood go up six times is almost certainly going to be a problem for patients." (Tr. 110:24-111:2). This discovery gave rise to the DDI patents, which "relate[] to methods involving avoiding adverse drug interactions with fluvoxamine and pirfenidone or other moderate to strong inhibitors of CYP enzymes." (JTX0005 at 1; JTX0007 at 1).

Claim 6 of the '383 patent is a dependent claim of unasserted independent claim 5, disclosing, "The method of claim 5, wherein the patient has idiopathic pulmonary fibrosis (IPF)." (JTX0005 at 13). Claim 5 of the '383 patent discloses:

> A method of administering pirfenidone therapy to a patient in need thereof, comprising first discontinuing administration of fluvoxamine to avoid an adverse drug interaction with pirfenidone, and then administering to the patient a therapeutically effective amount of pirfenidone.

(*Id.*).

Claim 3 of the '002 patent is a dependent claim of unasserted dependent claim 2, disclosing, "The method of claim 2 wherein the patient has idiopathic pulmonary fibrosis (IPF)." (JTX0007 at 13). Claim 2 of the '002 patent is a dependent claim of unasserted independent claim 1, disclosing, "The method of claim 1 wherein the pirfenidone is administered three times per day." (*Id.*). Claim 1 of the '002 patent discloses:

> A method of administering pirfenidone and fluvoxamine concurrently to a patient in need thereof comprising administering a therapeutically effective amount of pirfenidone to the patient, wherein the amount of the pirfenidone is about 801 mg/day.

(*Id.*).

Claim 9 of the '002 patent is a dependent claim of unasserted dependent claim 8, disclosing, "The method of claim 8 wherein the patient has idiopathic pulmonary fibrosis (IPF)." (*Id.*). Claim 8 of the '002 patent is a dependent claim of unasserted independent claim 6, disclosing, "The method of claim 6 wherein the pirfenidone is administered three times per day." (*Id.*). Claim 6 of the '002 patent discloses:

> A method of providing pirfenidone therapy to a patient in need thereof comprising titrating the dosage of pirfenidone administered to the patient downward from a dose of about 2400 mg/day, while co-administering with fluvoxamine, wherein the dose of pirfenidone is reduced by about 1600 mg/day.

(*Id.*).

II. LEGAL STANDARD

A. Infringement

A patent is directly infringed when a person "without authority makes, uses, offers to sell, or sells any patented invention, within the United States . . . during the term of the patent . . . ." 35 U.S.C. § 271(a). A two-step analysis is employed in making an infringement determination. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). First, the court must construe the asserted claims to ascertain their meaning and scope. *See id.* The trier of fact must then compare the properly construed claims with the accused infringing product. *See id.* at 976. This second step is a question of fact. *See Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1353 (Fed. Cir. 1998).

"Under § 271(b), whoever actively induces infringement of a patent shall be liable as an infringer." *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1363 (Fed. Cir. 2003). To prevail on a theory of induced infringement, a plaintiff must prove (1) direct infringement and (2) "that the defendant possessed specific intent to encourage another's infringement and not merely that the defendant had knowledge of the acts alleged to constitute infringement." *Vanda Pharm. Inc. v.*

West-Ward Pharm. Int'l Ltd., 887 F.3d 1117, 1129 (Fed. Cir. 2019) (quoting *DSU Med. Corp. v. JMA Co.*, 471 F.3d 1293, 1306 (Fed. Cir. 2006)).

In a Hatch-Waxman case, a plaintiff "can satisfy its burden to prove the predicate direct infringement by showing that if the proposed ANDA product were marketed, it would infringe the [asserted patent]." *Vanda*, 887 F.3d at 1130. For method-of-treatment patents, if an ANDA applicant's "proposed label instructs users to perform the patented method . . . , the proposed label may provide evidence of [the ANDA applicant's] affirmative intent to induce infringement." *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010). "When proof of specific intent depends on the label accompanying the marketing of a drug inducing infringement by physicians, the label must encourage, recommend, or promote infringement." *Vanda*, 887 F.3d at 1129 (cleaned up).

B. Obviousness

A patent is invalid as obvious under 35 U.S.C. § 103 if "the claimed invention as a whole would have been obvious to a person of ordinary skill in the art at the time the invention was made." *Kahn v. Gen. Motors Corp.*, 135 F.3d 1472, 1479 (Fed. Cir. 1998). "Obviousness is a question of law based on underlying factual findings: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) objective considerations of nonobviousness." *In re Morsa*, 713 F.3d 104, 109 (Fed. Cir. 2013) (citing *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17–18 (1966)).

To show a patent is obvious, a party "must demonstrate by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *InTouch Techs., Inc. v. VGO Commc'ns, Inc.*, 751 F.3d 1327,

1347 (Fed. Cir. 2014) (cleaned up). The overall inquiry into obviousness, though, must be "expansive and flexible." *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 415 (2007). In conducting the obviousness analysis, "a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at 418.

III. DISCUSSION

A. The LFT Patents

1. Infringement

Each method disclosed in the Asserted Claims of the LFT patents has three limitations: (1) pirfenidone administration for the treatment of IPF, (2) a patient having exhibited a Grade 2 elevation in one or more biomarkers of liver function (specifically, ALT and/or AST) following pirfenidone administration, and (3) a dose "modification."[4] The dose modifications disclosed in the Asserted Claims are:

(1) For claim 9 of the '729 patent, dose reduction to "doses lower than 2400 mg/day for a time period" followed by a return to the full dose of "2400 mg/day or 2403 mg/day";

(2) For claim 6 of the '707 patent, maintenance of the full dose of "2400 mg/day or 2403 mg/day";

(3) For claim 14 of the '707 patent, dose reduction to a dose of "1600 mg/day or 1602 mg/day";

(4) For claim 12 of the '462 patent, dose interruption "for about a week, or until biomarkers of liver function are within normal limits," followed by returning to a full dose of "2400 mg/day or 2403 mg/day";

[4] For clarity, I adopt the parties' non-literal use of the word "modification," even though one of the potential "modifications" is maintenance of the full dose.

(5) For claim 28 of the '462 patent, dose interruption "for about a week, or until biomarkers of liver function are within normal limits," followed by returning to a dose of "at least 1600 mg/day"; or

(6) For claim 19 of the '701 patent, dose reduction to "at least 1600 mg/day or 1602 mg/day."

Sandoz's proposed label includes, under the sub-heading "Dosage Modification due to Elevated Liver Enzymes," the following guidance for patients, depending upon whether they are asymptomatic or symptomatic, exhibiting Grade 2 liver enzyme elevations:

> ***Dosage Modification due to Elevated Liver Enzymes***
>
> Dosage modifications or interruptions may also be necessary when liver enzyme and bilirubin elevations are exhibited. For liver enzyme elevations, modify the dosage as follows:
>
> If a patient exhibits >3 but ≤5 × the upper limit of normal (ULN) ALT and/or AST without symptoms or hyperbilirubinemia after starting pirfenidone tablets therapy:
>
> - Discontinue confounding medications, exclude other causes, and monitor the patient closely.
> - Repeat liver chemistry tests as clinically indicated.
> - The full daily dosage may be maintained, if clinically appropriate, or reduced or interrupted (e.g., until liver chemistry tests are within normal limits) with subsequent re-titration to the full dosage as tolerated.
>
> If a patient exhibits >3 but ≤5 × ULN ALT and/or AST accompanied by symptoms or hyperbilirubinemia:
>
> - Permanently discontinue pirfenidone tablets.
> - Do not rechallenge patient with pirfenidone tablets.

(PTX00032 at 2).

The parties agree that Sandoz's label recommends using pirfenidone for the treatment of IPF and includes treatment instructions for patients exhibiting Grade 2 elevations in ALT and/or AST. (D.I. 374 at 3; D.I. 380 at 3). Indication and Grade 2 elevations, however, are only two of the three limitations of each Asserted Claim. Each claim also requires a dose modification, and the parties disagree over whether Sandoz's label "encourages, recommends, or promotes" any of the dose modifications disclosed in the Asserted Claims.

The third bullet point from the asymptomatic Grade 2 elevations sub-section of Sandoz's proposed label ("the Asymptomatic Section") presents five options: (1) maintaining the dose, (2) reducing the dose, (3) reducing the dose followed by re-titration to the full dose as tolerated, (4) indefinitely/permanently interrupting/discontinuing the dose,[5] and (5) interrupting the dose followed by re-titration to the full dose as tolerated. (PTX0032 at 2). The immediately following sub-section ("the Symptomatic Section") gives a single direction: "Permanently discontinue pirfenidone tablets. Do not rechallenge patients with pirfenidone tablets." (*Id.*).

Four of the five dose modification options provided in the Asymptomatic Section are covered by the Asserted Claims. The first option is covered by claim 6 of the '707 patent, the second by claim 14 of the '707 patent and claim 19 of the '701 patent, the third by claim 9 of the '729 patent, and the fifth by claims 12 and 28 of the '462 patent. The fourth option for asymptomatic patients and the only option for symptomatic patients, permanent discontinuation of pirfenidone, are not covered by any of the Asserted Claims.

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[5] Plaintiffs dispute that permanent discontinuation is an option included in the Asymptomatic Section of Sandoz's label. (D.I. 383 at 4 n.1). I find as a fact that this option is contemplated by the plain language of the label and that the testimony of Dr. Nathan and Dr. Morrow at trial confirms that a physician would interpret the label as presenting permanent discontinuation of pirfenidone as a potential option for both symptomatic and asymptomatic patients exhibiting Grade 2 ALT/AST elevations. (Tr. 249:10-250:14, 252:5-253:7 (Nathan), 325:9-18 (Morrow)).

In the Asymptomatic Section, the label states, the dosage may be "interrupted (e.g., *until liver chemistry tests are within normal limits*) with subsequent re-titration to the full dosage *as tolerated*." (PTX00032 at 2) (emphasis added). The clear implication of this is that in the event liver chemistry tests do not return to normal limits or re-titration is not tolerated by the patient, permanent discontinuation (*i.e.*, switching the patient to nintedanib) is an option. Dr. Nathan's testimony in response to questions about various treatment options "a pulmonologist reading the label" would have "when they've seen a patient that exhibits a grade 2 liver abnormality" confirms as much. (Tr. 251:21-253:3 ("Q. A fourth option is to discontinue Pirfenidone as we talked about if in the physician's judgment or in the patient's circumstances, that would be clinically appropriate; right? A. Correct.")).

Plaintiffs argue that the five dose modification options included in the third bullet point of the Asymptomatic Section are recommendations. (D.I. 374 at 5-6). Thus, they contend, because four of the five options are covered by the Asserted Claims, "Sandoz's inclusion of [these] recommendation[s] in its Proposed Label shows its intent to induce infringement." (*Id.*). Sandoz argues that because "Sandoz's label does not affirmatively encourage the use of any patented method of treatment," and at most merely "describes or permits certain infringing methods *as well as describing and permitting non-infringing* methods of treatment," Plaintiffs cannot prove intent to induce infringement. (D.I. 380 at 3). I agree with Sandoz for the following reasons.

First, while the Asymptomatic Section lists some dose modifications covered by the Asserted Claims as potential treatment options, it does not affirmatively recommend any of them. There is a clear contrast between the directive language used in the first two bullet points of the Asymptomatic Section and the permissive language used in the third bullet point. The first two bullet points begin with active-voice verbs: "Discontinue confounding medications . . . ," "Repeat liver chemistry tests . . . ." (PTX0032 at 2). They are directions. By contrast, the third bullet point uses a passive-voice verb and does not begin with it: "The full daily dosage may be maintained . . . ." (*Id.*). The third bullet point does not direct anyone to do anything. The use of "may" shows that it merely presents options. Indeed, it describes multiple options, to wit, maintaining, reducing, interrupting, or discontinuing. "Merely describing an infringing mode is not the same as recommending, encouraging, or promoting an infringing use, or suggesting that an infringing use 'should' be performed." *Takeda Pharms. U.S.A., Inc. v. West-Ward Pharm. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015) (cleaned up).

Second, the proposed label does affirmatively recommend some dose modifications for patients exhibiting Grade 2 ALT/AST elevations, but they are non-infringing modifications. The

wording of the third bullet point of the Asymptomatic Section is even more conspicuous when contrasted with the wording of the Symptomatic Section. The Symptomatic Section provides clear directions: "Permanently discontinue pirfenidone tablets," "Do not rechallenge patient with pirfenidone tablets." (PTX0032 at 2). Unlike the "Dosage Modification due to Elevated Liver Enzymes" section of the proposed label, the claimed methods do not distinguish between symptomatic and asymptomatic patients. Thus, the only dose modification that is expressly "recommended" by the proposed label in the face of a Grade 2 ALT/AST elevation – permanently discontinuing pirfenidone treatment – refers to the same situation as, but is not covered by, the methods of the Asserted Claims.

Plaintiffs argue the Federal Circuit's decision in *Teva* "disproves Sandoz's theory" that the listing of several possible options is not equivalent to recommending any one option. (D.I. 374 at 6-7). In *Teva*, the Court rejected Teva's argument that inducement cannot be found where a label "encourage[s] both infringing and noninfringing uses." (D.I. 374 at 7-8 (citing *GlaxoSmithKline LLC v. Teva Pharms. USA, Inc.*, 7 F.4th 1320, 1329-30 (Fed. Cir. 2021), *reh'g en banc denied*, 25 F.4th 949 (Fed. Cir. 2022) (per curiam))). The relevant facts in *Teva*, however, are easily distinguishable from the relevant facts here, because Sandoz's label does not "encourage both infringing and noninfringing uses." Unlike in *Teva*, where "substantial evidence" supported "the jury's determination that Teva's partial label contained information encouraging each claimed step," here, the label only recommends discontinuation, which is a non-infringing use. *Teva*, 7 F.4th at 1330. The infringing uses are presented as options, not recommendations.

The facts here are more closely analogous to the facts in *HZNP*, another ANDA labeling case in which the Federal Circuit considered whether language in Actavis's label for a topical medication induced infringement of Horizon's method patent. There, the patented method required

three steps: (1) applying the topical medication, (2) waiting for the area to dry, and (3) applying "sunscreen, insect repellant, or a second topical medication." *HZNP Meds. LLC v. Actavis Lab'ys UT, Inc.*, 940 F.3d 680, 702 (Fed. Cir. 2019). The relevant portion of Actavis's label stated, "Wait until the treated area is dry before applying sunscreen, insect repellant, lotion, moisturizer, cosmetics, or other topical medication to the same knee you have just treated with [the topical medication]." *Id.* at 700.

The Court held that Actavis's label did not "encourage infringement," because (1) "the label does not require subsequent application of sunscreen, insect repellant, or a second medication," and (2) "Actavis's label is broader than step three of Horizon's claimed method" because it warns about "clothing, cosmetics, lotion, water, moisturizer, and other substances" in addition to "sunscreen, insect repellant, or another topical medication." *Id.* at 702. For those reasons, the Court concluded that although the evidence "establishe[d] that some users might infringe," it did "not establish that 'the proposed label instructs users to perform the patented method.'" *Id.*

Similarly, here, (1) Sandoz's label does not require that any one of the claimed dose modifications be undertaken,[6] and (2) the dose modification step in Sandoz's label is "broader"

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[6] Another notable similarity between *HZNP* and the present case is that treatment of IPF patients with pirfenidone giving rise to the patented methods is only a subset of treatment of IPF patients with pirfenidone. In *HZNP*, the plaintiff "recognize[d] that not every user will need to apply sunscreen, insect repellant, or another topical medication." *Id.* at 701. Here, the subset of patients with whom the claimed methods will be implicated is even smaller. As Sandoz notes, the vast majority (roughly 96%) of patients using pirfenidone do not experience Grade 2 elevations in ALT/AST. (D.I. 380 at 10; Tr. 149:10-15, 268:2-269:12).

While a high prevalence of non-infringing uses is not dispositive on the issue of inducement, I agree with Sandoz that, especially in an ANDA context, it is relevant to the inquiry. *See Eli Lilly & Co. v Teva Parenteral Meds., Inc.*, 845 F.3d 1357, 1368 (Fed. Cir. 2017) ("[W]e have not required evidence regarding the general prevalence of the induced activity."); *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1363-66 (Fed. Cir. 2003) ("Especially where a

than those in the patented methods, as the label also suggests dose modification options (*e.g.*, permanent discontinuation) not covered by the Asserted Claims. While the evidence presented at trial confirmed that some physicians will infringe by implementing a dose modification covered by one of the Asserted Claims (*e.g.*, Tr. 356:11-357:3), the evidence did not establish that Sandoz's proposed label encourages, recommends, or promotes infringement of the patented methods.

Sandoz's label merely provides physicians with multiple dose modification options, some covered by the Asserted Patents and some not, and leaves it to the physician's clinical judgment to determine how to modify the patient's dosage. Because Plaintiffs have not shown that Sandoz's label evinces a specific intent to induce infringement of the LFT patents and Plaintiffs presented no other evidence of Sandoz's specific intent, Plaintiffs have not met their burden of proving infringement with respect to the LFT patents.

2. Invalidity

The Asserted Claims of the LFT patents require (1) the administration of pirfenidone to treat IPF, where a "full" dose is 2400 or 2403 mg/day, (2) the presence of liver enzyme elevations

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product has substantial noninfringing uses [97.9% of prescriptions], intent to induce infringement cannot be inferred even when the defendant has actual knowledge that some users of its product may be infringing the patent."); *Caraco Pharm. Lab'ys, Ltd. v. Novo Nordisk A/S*, 566 U.S. 399, 414-15 (2012) ("[A] single drug may have multiple methods of use, only one or some of which a patent covers . . . . The [Hatch-Waxman] statutory scheme [] contemplates that one patented use will not foreclose marketing a generic drug for other unpatented ones.").

In *Vanda*, the Federal Circuit rejected the defendant's argument that *Warner-Lambert* stands for the proposition that the presence of substantial non-infringing uses necessarily precludes a finding of inducement, because "the proposed label itself recommend[ed] infringing acts." *Vanda Pharms. Inc. v. West-Ward Pharms. Int. Ltd.*, 887 F.3d 1117, 1132-33 (Fed. Cir. 2018). Here, by contrast, Plaintiffs have not proven that the proposed label recommends infringing acts. The Court in *Vanda* clarified that because the § 271(c) "substantial noninfringing uses" statutory defense to contributory infringement is not present as a defense to § 271(b) induced infringement, "a person can be liable for inducing an infringing use of a product even if the product has substantial noninfringing uses." *Id.* at 1133. *Vanda* did not go so far as to say the presence of substantial noninfringing uses is irrelevant to the inducement inquiry altogether.

in a patient, and (3) a dose modification, including maintenance of the dose ('707 patent cl. 6), dose reduction ('707 cl. 14, '701 patent cl. 19), reducing the dose followed by re-titration to the full dose ('729 patent cl. 9), or interrupting the dose followed by re-titration to at least a reduced dose or the full dose ('462 patent cls. 12, 28).

Sandoz argues, "Each of [the LFT patent] claims is invalid for obviousness under 35 U.S.C. § 103 in view of Azuma and optionally the Pirespa Label." (D.I. 376 at 4). The parties agree that the Azuma Article and the Pirespa Label are prior art. (*See* D.I. 378 at 1). Plaintiffs respond, however, that the Asserted Claims are not obvious because (1) the prior art did not establish the efficacy of pirfenidone for the treatment of IPF, (2) the prior art did not disclose continued use of pirfenidone after a Grade 2 elevation in AST/ALT and a POSA would not have had a reasonable expectation of success in doing so, and (3) Sandoz improperly uses hindsight to arrive at the claimed dosage amounts from what was disclosed in the prior art. (*Id.* at 2-15). For the following reasons, I agree with Sandoz that the Asserted Claims of the LFT patents are invalid for obviousness over the Azuma Article, the Pirespa Label, and standard practice generally disclosed in the prior art.

a. Efficacy for Treatment of IPF

I find that as of November 10, 2008, the priority date for the LFT patents (D.I. 331-1 ¶¶ 49, 53, 59, 64, 77, 78, 88, 89), a POSA would have known that pirfenidone had efficacy for the treatment of IPF. In October 2008, PMDA, the regulatory authority tasked with approving drug products in Japan, approved pirfenidone for the treatment of IPF. (JTX0029 at 5; JTX0030 at 4). PMDA based its approval on the results of a Phase III study conducted by Shionogi. (JTX0030 at 4 ("[PMDA] has concluded that the data and information submitted demonstrate the efficacy and safety of [pirfenidone] for use in the treatment of idiopathic pulmonary fibrosis. PMDA has

concluded that an acceptable level of clinical efficacy of [pirfenidone] has been demonstrated in the data from the Phase III studies . . . .")). At the time of its approval, PMDA publicly released a label for Pirespa containing detailed instructions for using pirfenidone to treat IPF ("the Pirespa Label") (JTX0029) and the "2008 Pirfenidone Report" (JTX0030), which summarized the efficacy and safety data supporting PMDA's approval of the drug.

A 2005 Phase II study, the results of which were published in a peer-reviewed article ("the Azuma Article") (JTX0031), also reported promising results regarding the efficacy of pirfenidone in treating IPF. The Azuma Article reported "positive treatment effects on vital capacity," which is "the single best measure of IPF lung function," and decreases in "episodes of acute exacerbations of IPF," which are characterized by "very rapid deterioration of lung function . . . associated with a very high mortality, at least 90 or 95 percent in severe cases." (Tr. 455:12-456:11 (Duncan)). The Azuma Article concluded, "[T]his novel study provides encouraging evidence to pursue the potential of an efficacious treatment with pirfenidone for patients with IPF in a well designed phase III clinical trial." (JTX0031 at 7).

Plaintiffs point to the lack of FDA-approved treatments for IPF in the United States as of the priority date and "safety concerns [regarding pirfenidone], including severe liver toxicity" in support of their argument that a POSA would not have known pirfenidone had efficacy for the treatment of IPF. (D.I. 378 at 2-4). Lack of U.S. regulatory approval of a drug for the treatment of IPF and the presence of safety concerns relating to pirfenidone, however, are irrelevant to the fact that, as of the priority date, the prior art was replete with evidence of pirfenidone's effectiveness in the treatment of IPF. The data reported in the Azuma Article and the materials supporting PMDA's approval of pirfenidone for the treatment of IPF would have motivated a POSA to continue investigating pirfenidone as a treatment for IPF, with a reasonable expectation of success.

b. Continued Use after Grade 2 ALT/AST Elevation

I find that the specific dose modifications claimed in the LFT patents would have been obvious over the disclosures of the Azuma Article and the Pirespa Label, combined with known, standard medical practices. Both the Azuma Article and the Pirespa Label expressly disclose continuing pirfenidone administration in patients exhibiting elevated liver enzymes. The evidence at trial showed it was well-known in the art that continuation of drug administration generally in patients with elevated liver enzymes was feasible, potentially following a temporary reduction or interruption in dosage.

The Azuma Article disclosed, "For an adverse event of Grade 2 or worse, the dosage [of pirfenidone] was reduced in a stepwise manner . . ." as long as symptoms persisted. (JTX0031 at 3). Patients were monitored for fourteen-day periods following each stepwise dose reduction. (*Id.*). "When the adverse event of Grade 2 or worse persisted or increased despite reducing the dosage . . . , the study medication was discontinued . . . ." (*Id.*). "If the adverse event had resolved or decreased with reduction in the dose," the patient's dose was increased back to the original amount. (*Id.*). The Article lists "Elevation of [AST]"[7] among the "adverse events" observed in study patients. (*Id.* at 6). The Article reports observing these elevations in a total of ten patients but only one patient was discontinued from the study for "abnormality of hepatic function." (*Id.*). Although the Article does not specify how many of these AST elevations were Grade 2 elevations, I find that a POSA would have reasonably concluded based on the fact that ten elevations were reported and only one patient was discontinued for liver-function related reasons, that the majority of patients exhibiting Grade 2 elevations in AST were treated in accordance with the study's dose

[7] The Azuma Article refers to "Elevation of GOT." (JTX0031 at 6). As Dr. Nathan confirmed, "GOT is another name for AST." (Tr. 682:22-23).

reduction and re-escalation protocol for managing "Grade 2 adverse events." (*See* Tr. 471:12-472:12 (Duncan)).

The Pirespa Label also disclosed dose reduction as an option for continuing pirfenidone treatment in patients exhibiting elevated AST and ALT unaccompanied by jaundice. (JTX0029 at 6). Section 3 of the Pirespa Label, "Adverse Reactions," is divided into two sub-sections, "Clinically significant adverse reactions," and "Other adverse reactions." The relevant portion of the label reads:

> **3. Adverse Reactions**
>
> Out of 265 cases evaluated for safety before NDA approval, adverse reactions were observed in 233 cases (87.9%). Main adverse reactions were photosensitivity (137 cases, 51.7%), anorexia (61 cases, 23.0%), stomach discomfort (37 cases, 14.0%), and nausea (32 cases, 12.1%).
>
> Abnormal changes in clinical laboratory test values were observed in 120 cases (45.3%) among 265 cases evaluated for safety. The change of clinical laboratory test value mainly observed was increased γ-GTP (53 cases, 20.0%).
>
> **(1) Clinically significant adverse reactions**
>
> **Hepatic function disorders and jaundice (less than 0.1-1%):** Since hepatic function disorders accompanied by increased AST (GOT), ALT (GPT), etc. and jaundice may occur and result in hepatic failure, the patient's state should be fully observed by periodic examination, etc. If any abnormalities are observed, administration should be discontinued and appropriate therapeutic measures should be taken.
>
> **(2) Other adverse reactions**
>
> If the following adverse reactions occur, appropriate therapeutic measures such as dose reduction or discontinuation of administration should be performed as necessary.

(JTX0029 at 6).

The following table immediately follows the "Other adverse reactions" section and is not preceded by its own sub-heading.

Incidence / Body system	≥ 5%	1% ≥ < 5%	< 1%
Dermatologic	photosensitivity (51.7%), rash	itching, erythema, eczema, lichen planus	
Gastrointestinal	anorexia (23.0%), stomach discomfort (14.0%), nausea (12.1%), diarrhea, heartburn	abdominal fullness, vomiting, constipation, reflux esophagitis, stomatitis, abdominal discomfort, abdominal pain, cheilitis	labial erosion
Cardiovascular		palpitation	
Psychoneurologic	sleepiness, dizziness, stagger (wooziness)	headache, headache dull	
Hepatic	increased γ-GTP (20.0%), increased AST (GOT), increased ALT (GPT), increased Al-P, increased LDH	increased bilirubin	
Hematologic		leukocytosis, eosinophilia, leukopenia	thrombocytopenia
Others	malaise	weight loss, fever, dysgeusia, musculoskeletal pain, hot flash	

(*Id.*).

For clarity, the layout of the entire relevant page from the Pirespa Label is shown below.

PRECAUTIONS

1. **Careful Administration (Pirespa® should be administered with care in the following patients.)**
   (1) Patients with hepatic impairment [risk of worsening hepatic impairment.]
   (2) Patients with renal impairment [Use experiences in such patients are not enough.]
   (3) Elderly patients [see "Use in the Elderly."]
2. **Important Precautions**
   (1) **Photosensitivity may occur and there is the possibility of carcinogenesis of the skin accompanied by light exposure.** When this drug is administered, a patient should be adequately instructed on in advance.
      1) In the case of going out of the home, protection measures against light exposure should be taken such as avoiding ultraviolet ray by wearing long-sleeved clothes and a hat, or using a parasol or a sunscreen with high sunscreening effects (SPF50+, PA+++). [Refer to the item "Other Precautions."]
      2) If skin abnormalities such as rash and itching are observed, contact a physician immediately.
   (2) Since Pirespa may induce sleepiness, dizziness or stagger, a patient should be cautioned against engaging **in potentially hazardous activities requiring alertness, such as operating machinery or driving a car.**
   (3) **Hepatic function disorders** accompanying increased AST (GOT), ALT (GPT), etc. and **jaundice** may occur. Periodic examination should be performed during administration of this drug and the patient's state should be fully observed. [Refer to the item "Clinically significant adverse reactions."]
3. **Adverse Reactions**
   Out of 265 cases evaluated for safety before NDA approval, adverse reactions were observed in 233 cases (87.9%). Main adverse reactions were photosensitivity (137 cases, 51.7%), anorexia (61 cases, 23.0%), stomach discomfort (37 cases, 14.0%), and nausea (32 cases, 12.1%).
   Abnormal changes in clinical laboratory test values were observed in 120 cases (45.3%) among 265 cases evaluated for safety. The change of clinical laboratory test value mainly observed was increased γ-GTP (53 cases, 20.0%).
   (1) **Clinically significant adverse reactions**
   Hepatic function disorders and jaundice (less than 0.1-1%): Since hepatic function disorders accompanied by increased AST (GOT), ALT (GPT), etc. and jaundice may occur and result in hepatic failure, the patient's state should be fully observed by periodic examination, etc. If any abnormalities are observed, administration should be discontinued and appropriate therapeutic measures should be taken.
   (2) **Other adverse reactions**
   If the following adverse reactions occur, appropriate therapeutic measures such as dose reduction or discontinuation of administration should be performed as necessary.

Incidence / Body system	≥ 5%	1% ≤ · < 5%	< 1%
Dermatologic	photosensitivity (51.7%), rash	itching, erythema, eczema, lichen planus	
Gastrointestinal	anorexia (23.0%), stomach discomfort (14.0%), nausea (12.1%), diarrhea, heartburn	abdominal fullness, vomiting, constipation, reflux esophagitis, stomatitis, abdominal discomfort, abdominal pain, cheilitis	labial erosion
Cardiovascular		palpitation	
Psychoneurologic	sleepiness, dizziness, stagger (wooziness)	headache, headache dull	
Hepatic	increased γ-GTP (20.0%), increased AST (GOT), increased ALT (GPT), increased ALP, increased LDH	increased bilirubin	
Hematologic		leukocytosis, eosinophilia, leukopenia	thrombocytopenia
Others	malaise	weight loss, fever, dyspnea, musculoskeletal pain, hot flash	

4. **Use in the Elderly**
   Since the elderly has decreased physiological function in general, this drug should be carefully administered.
6. **Use during Pregnancy, Delivery or Lactation**
   (1) It is desirable not to administer this drug to a pregnant woman or possibly pregnant woman. [In rats, prolongation of gestational period, decreased birth rate, and drug transfer to a fetus have been observed. In rabbits, abortion or premature birth has been observed. In both animal studies, teratogenicity has not been observed[1,2].]
   (2) A lactating woman should avoid lactation during administration of this drug. [In rats, drug transfer to milk and inhibition of weight gain of offspring after mid-term lactation have been observed[2,3].]
6. **Pediatric Use**
   The safety of this drug in low birth weight infants, neonates, nursing infants, infants and children has not yet been established. [no clinical experience]
7. **Precautions concerning Use**
   Precautions regarding dispensing: For drugs that are dispensed in a press-through package (PTP), instruct the patient to remove the drug from the package prior to use. (It has been reported that, if the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa, resulting in severe complications such as mediastinitis.)
8. **Other Precautions**
   (1) In a light chromosomal abnormality test using cultured cells derived from Chinese hamster lung, chromosome structure abnormality inducibility caused by light exposure has been observed. Since there is no difference between plasma concentration inducing phototoxicity

(*Id.*).

A plain reading of the "Adverse Reactions" section makes clear that the Pirespa Label distinguishes between increased AST and ALT accompanied by jaundice (Section 3(1)), and increased ALT/AST standing alone (Section 3(2)). For the former, the label instructs

discontinuation; for the latter, the label instructs dose reduction or discontinuation "as necessary." (*See* Tr. 465:20-469:23 (Duncan)). Plaintiffs' argument that the Section 3(1) instructions for "Clinically significant adverse reactions" also apply to adverse reactions the label differentially categorizes as "Other adverse reactions" in Section 3(2) defies common sense. (D.I. 378 at 5-8). The sentence immediately preceding the table expressly states its instructions are for a situation in which "*the following* adverse reactions occur." (JTX0029 at 6) (emphasis added).

Moreover, if the table were meant to include all adverse reactions including the clinically significant ones disclosed in Section 3(1), as Plaintiffs appeared to argue at trial, one would expect "hepatic function disorders and jaundice" to appear in the third column of the "Hepatic" row for adverse reactions occurring in <1% of patients. (*See* Tr. 826:4-830:25). Instead, that cell is blank. (JTX0029 at 6). Thus, a POSA reading the Pirespa Label would logically interpret the contents of the table as being limited to "Other adverse reactions." The POSA would conclude based on the inclusion of increased AST and ALT in the table that such increases, when not accompanied by jaundice, should not be considered "clinically significant adverse reactions" requiring discontinuation.

The 2008 Pirfenidone Report confirms that, although ALT increases were observed in seventeen patients[8] during Shionogi's Phase III study, increased ALT and/or AST values resulted in discontinuation of the study medication in only three patients. (JTX0030 at 53-54). Thus, most (14/17) patients with abnormal elevations in liver enzymes including ALT and AST were continued on pirfenidone treatment.

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[8] AST increases were observed in twelve patients. Presumably, there was some overlap between patients exhibiting ALT increases and patients exhibiting AST increases.

Plaintiffs argue Sandoz has an elevated burden of proof for proving invalidity, because "the Examiner closely examined the Pirespa Label and read it the way Plaintiffs do." (D.I. 378 at 7). I am not persuaded by this argument. That the Examiner agreed with Plaintiffs' strained interpretation of the Pirespa Label makes no difference here – by showing that the Examiner's interpretation is erroneous, Sandoz has met its "added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job . . . ." (*See* D.I. 378 at 7; *Shire LLC v. Amneal Pharm., LLC*, 802 F.3d 1301, 1307 (Fed. Cir. 2015) (quoting *PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1304 (Fed. Cir. 2008))).

Finally, I find that the dose adjustment protocols for managing liver enzyme elevations disclosed in the Azuma Article and Pirespa Label were consistent with standard medical practice as of the priority date. At that time, dose reductions, interruptions, and rechallenging were well-known strategies for treating patients exhibiting Grade 2 elevations of liver enzymes with other drugs. (Tr. 452:19-454:22 (Duncan) (highlighting examples of three drugs whose labels included "specific instruction or information about how to manage LFT abnormalities" as of 2008, including dose modifications followed by rechallenging); DTX0027 at 1, 4, 8-9 (Actimmune); DTX0142 at 21-22 (Gleevec); DTX0263 at 1, 13-14 (Tarceva); Tr.448:2-449:24 (Duncan) (confirming FDA DILI guidance did not recommend stopping administration of a drug for Grade 2 abnormalities in LFTs), 451:17-452:18 (Duncan) (discussing 2005 and 2007 references teaching that drug cessation in response to drug-induced mild reversible liver injury, including a grade 2 abnormality in ALT and AST alone, would "unnecessarily deny patients a potentially important therapy.")).

The U.S. Department of Health and Human Services' October 2007 "Guidance for Industry Drug-Induced Liver Injury" counsels, "Because transient rises and falls of ALT or AST are common, and progression to severe DILI or acute liver failure is uncommon, automatic

discontinuation of study drug upon finding a greater than 3xULN [upper limit of normal] elevation of ALT or AST may be unnecessary," stressing, "For most people, the liver appears capable of adapting to injury by foreign chemical substances . . . ." (DTX0144 at 11-12). The evidence shows that the prior art taught not to cease administration of a drug generally, or pirfenidone specifically, based solely upon a moderate elevation of ALT/AST without additional signs of drug-induced liver injury, such as elevated bilirubin. (DTX0144 at 12; Tr. 477:17-22, 483:16-484:7 (Duncan)).

Based on these disclosures in the prior art, a POSA would have had a reasonable expectation of success in continuing to treat patients exhibiting Grade 2 liver enzyme elevations with pirfenidone.

c. Dosage Amount

I find that the dosage amounts claimed in the present invention are obvious in light of the dosages disclosed in the Azuma Article and the Pirespa Label, and what was known about the average weight difference between the Japanese and American patient populations.

Both the Pirespa Label and the Azuma Article disclosed the use of a standard dosage of 1800 mg/day of pirfenidone for the treatment of IPF. (JTX0029 at 5; JTX0031 at 3). Undisputed evidence presented at trial showed it was known that an 1800 mg/day dosage in Japanese patients would be equivalent to 2400 mg/day for American patients, who, on average, weigh 30% more than Japanese patients. (Tr. 283:24-286:10 (Samuels) (confirming "the selected Pirfenidone dose of 2,403 milligrams per day was based on a calculation that adjusted for the difference in mean weights in the North American and European patient population compared with the Japanese patient population.")). "[T]he [dose] adjustment was approximately 30 percent because [] North American and European patients are approximately 30 percent heavier than Japanese patients of similar age." (Tr. 285:21-25 (Samuels)).

Moreover, as of the priority date, a clinical trial was underway in the United States using a maximum dosage of 2403 mg/day of pirfenidone. (Tr. 284:2-285:25 (Samuels); JTX0030 at 1, 60 ("[T]he ongoing clinical study conducted outside of Japan is verifying the suitability of a high dose of 2403 mg/day . . . .)). InterMune's Patent Application, "Method of Providing Pirfenidone Therapy to a Patient," published on August 14, 2008, two months before the priority date, disclosed using escalating doses of 801, 1,602, and 2,403 mg/day to administer pirfenidone to patients in the United States. (Tr. 464:4-465:12 (Duncan); JTX0034 at 11).

d. Secondary Considerations

Plaintiffs cite the "long-felt need for treatments for IPF," "skepticism both about the potential efficacy of pirfenidone and about continuing to treat patients who experience a grade 2 liver abnormality," teaching away from the claimed invention in the prior art, and "evidence of copying" by Sandoz and Shionogi as secondary considerations of non-obviousness with respect to the LFT patents. (D.I. 374 at 14-18). I do not find Plaintiffs' arguments persuasive for the following reasons.

Evidence relating to "Pirfenidone's arduous road to approval" is irrelevant to the LFT patents. The inventive element of the claimed methods is not that pirfenidone is effective for the treatment of IPF, but rather that patients exhibiting liver enzyme elevations can safely continue pirfenidone treatment. This is made clear by the fact that none of the Asserted Patents include any evidence of pirfenidone's efficacy in treating IPF beyond citing to the prior art. (JTX0001-JTX0004). Plaintiffs' narrative about the "long-felt need for treatments for IPF" and "Pirfenidone's arduous road to approval" is an inspiring one, but ultimately unrelated to whether the LFT management methods disclosed in the LFT patents were obvious. Similarly, Plaintiffs' evidence of the "failure of others" focuses on the general absence of an FDA-approved treatment for IPF,

rather than a specific failure to find a way to continue pirfenidone treatment in patients exhibiting liver enzyme elevations. (D.I. 374 at 15).

In support of their argument that there was skepticism "about continuing to treat patients who experience a grade 2 liver abnormality," Plaintiffs reference a quote by Dr. Wise, a pulmonologist on the data monitoring committee for InterMune's clinical trials, observing "that there was not much to gain from re-challenging these patients, but potentially there was a lot to lose." (*Id.* at 16; PTX0180 at 4). I find, however, that, at best for Plaintiffs, the evidence presented at trial showed it is unclear whether Dr. Wise's concern about "these patients" was in reference to patients exhibiting Grade 2 LFT abnormalities or patients exhibiting more serious LFT abnormalities – *i.e.*, Grade 3 and above. (PTX0180 at 4; Tr. 141:17-144:12 (Bradford), 369:8-370:6 (Wise)). Dr. Wise's statement is unhelpful for Plaintiffs.

Plaintiffs point to the Examiner's finding "that the prior art [the Pirespa Label] 'criticizes, discredits, and discourages' the inventive methods, [] that the prior art taught away from the inventions, and that it was unexpected that patients could continue treatment as claimed without suffering irreversible liver damage" as additional evidence of skepticism and teaching away. (D.I. 374 at 17 (citing JTX0010 at 245)). As discussed above (*supra* Part III.A.2.b.), however, I disagree that the Pirespa Label categorically taught away from continuing to treat patients exhibiting Grade 2 liver enzyme elevations. By "categorically," I mean the label does teach away from continuing to treat *symptomatic* patients exhibiting Grade 2 elevations, but does not teach away from continuing to treat *asymptomatic* patients exhibiting Grade 2 elevations. Therefore, I do not find Plaintiffs' argument about the Examiner's findings persuasive as a secondary consideration of non-obviousness.

Finally, I agree with Sandoz that evidence of copying is particularly unpersuasive in ANDA cases, where generic companies have a clear regulatory incentive to exactly replicate the brand name drug's label. (D.I. 380 at 23 (citing *Aventis Pharma S.A. v. Hospira, Inc.*, 743 F. Supp. 2d 305, 349 (D. Del. 2010)). Thus, I do not accord any weight to the language of Sandoz's proposed label. Plaintiffs also appear to argue Shionogi made changes to its label in response to the LFT patents. (D.I. 374 at 18). I find that this claim is not supported by the evidence. As discussed above, I find that the language of the original Pirespa Label allowed for the continued treatment of patients exhibiting liver enzyme elevations. (JTX0029 at 6).

3. Conclusion

For the reasons stated above, I find that Plaintiffs have not proven infringement by a preponderance of the evidence. I further find that Sandoz has proven by clear and convincing evidence that the Asserted Claims of the LFT Patents are invalid as obvious.

B. The DDI Patents

1. Infringement

The Asserted Claims of the DDI patents have the following limitations: (1) a patient being treated with pirfenidone for IPF, (2) the patient also being treated with fluvoxamine during or immediately prior to pirfenidone treatment, and (3) a dose modification. The dose modifications include: (1) for claim 6 of the '383 patent, discontinuation of fluvoxamine prior to administration of pirfenidone, (2) for claim 3 of the '002 patent, concurrent administration of fluvoxamine and pirfenidone "wherein the amount of the pirfenidone is about 801 mg/day," administered three times per day, and (3) for claim 9 of the '002 patent, concurrent administration of fluvoxamine and pirfenidone wherein the dosage of pirfenidone, administered three times per day, is titrated downward "from a dose of about 2400 mg/day" for a total reduction of "about 1600 mg/day."

Sandoz's proposed label warns about potential drug-drug interactions with fluvoxamine in three places. First, under the "Drug Interactions" sub-heading of the label's "Highlights of Prescribing Information," the label states, "Discontinue fluvoxamine prior to administration of pirfenidone or reduce [pirfenidone] to 267 mg three times a day," for a total of 801 mg/day. (PTX0032 at 1). Second, in Section 2.4, "Dosage Modification due to Drug Interactions," under the sub-heading, "Strong CYP1A2 Inhibitors (e.g., fluvoxamine, enoxacin)," the label states, "Reduce pirfenidone tablets to 267 mg three times a day (801 mg/day)." (*Id.* at 3). Finally, in Section 7.1, "CYP1A2 Inhibitors," under the sub-heading, "Strong CYP1A2 Inhibitors," the label states:

> The concomitant administration of pirfenidone and fluvoxamine or other strong CYP1A2 inhibitors (e.g., enoxacin) is not recommended because it significantly increases exposure to pirfenidone *[see Clinical Pharmacology (12.3)]*. Use of fluvoxamine or other strong CYP1A2 inhibitors should be discontinued prior to administration of pirfenidone and avoided during pirfenidone treatment. In the event that fluvoxamine or other strong CYP1A2 inhibitors are the only drug of choice, dosage reductions are recommended. Monitor for adverse reactions and consider discontinuation of pirfenidone as needed *[see Dosage and Administration (2.4)]*.

(*Id.* at 5).

Plaintiffs argue, "If Sandoz sells its ANDA product, it will do so with a label that explicitly recommends practicing the claimed methods, and it therefore induces infringement of the fluvoxamine patents." (D.I. 374 at 10). Sandoz responds that Plaintiffs have not proven induced infringement for three reasons: (1) "there is no evidence of likely direct infringement," (2) "Plaintiffs have failed to demonstrate that Sandoz intends to induce infringement," and (3) "the law concerning divided infringement [] prevents a finding of liability" because "even if all the steps of the claimed method were carried out, they would not be attributable to a single actor." (D.I. 380 at 12). Because I agree with Sandoz that Plaintiffs have failed to prove direct

infringement, a prerequisite for a finding of induced infringement, I do not reach Sandoz's arguments relating to intent to induce and divided infringement.

Plaintiffs argue, "in an ANDA case, a proposed label that recommends an infringing use is sufficient evidence ***both*** that there will be direct infringement ***and*** that the ANDA applicant has the intent to induce that infringement." (D.I. 374 at 10). Plaintiffs are mistaken. The presence of language that "encourages, recommends or promotes" an infringing use on a proposed label, without any additional evidence showing such an infringing use will in fact occur, especially where there is evidence that an infringing use likely will not occur, is insufficient for a finding of induced infringement. While it is true "a patentee does not need to prove an actual past instance of direct infringement by a physician to establish infringement" in an ANDA case, Plaintiffs still must prove, by a preponderance of the evidence, that "if a particular drug *were* put on the market, it *would* infringe the relevant patent."[9] *Vanda Pharms. Inc. v. West-Ward Pharms. Int. Ltd.*, 887 F.3d 1117, 1129-30 (Fed. Cir. 2018). Plaintiffs have not done that.

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[9] In *Vanda*, the case Plaintiffs cite as support for their contention that language on the proposed label is sufficient evidence to prove both inducement and direct infringement, the district court expressly relied on evidence beyond the label about the real-world practice of physicians to reach its conclusion that direct infringement would likely occur. *Vanda Pharms. Inc. v. Roxane Lab'ys, Inc.*, 203 F. Supp. 3d 412, 433 (D. Del. 2016) ("Dr. Alva's patient records and testimony confirm that he has practiced the steps of the '610 Patent claims.").

Plaintiffs also cite *Eli Lilly* as support for their contention that a label on its own is sufficient evidence for a finding of induced infringement. (D.I. 374 at 11). Plaintiffs cite, however, to the discussion of the label's relevance to "affirmative intent to infringe the patent," rather than the discussion of direct infringement. (*Id.* (citing *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357, 1368 (Fed. Cir. 2017))). In its direct infringement analysis, the Court of Appeals notes, "the district court relied *in part* on Defendants' proposed product labeling as evidence of infringement," and ultimately concludes, "The product labeling, combined with the testimony discussed above [about physicians' general practices], provide sufficient evidence that physicians condition premetrexed treatment on [the patient's performance of the patented method, satisfying the first prong of the *Akamai* test for proving direct infringement under a theory of divided infringement]." *Eli Lilly*, 845 F.3d at 1364-68 (emphasis added).

Direct infringement of the DDI patents requires that a patient either take fluvoxamine and pirfenidone concurrently or stop fluvoxamine treatment in order to begin pirfenidone treatment. There was no evidence at trial of any patient receiving pirfenidone after being prescribed fluvoxamine, or of any patient taking fluvoxamine and pirfenidone concurrently. In fact, all three medical experts testified that in the seven years pirfenidone has been available for treatment of IPF in the United States, none of them has had a single patient receive fluvoxamine before taking pirfenidone or receive both concurrently. (Tr. 261:3-8 ("Q. . . . [I]n your 30-some-odd years of practicing, you don't recall a single patient that you've treated for IPF who was taking fluvoxamine; correct? A. That's correct.") (Nathan); Tr. 334:7-12 ("Q. . . . [H]ow common is it for IPF patients who take Pirfenidone to have taken fluvoxamine? A. I've never seen it. Q. Have you ever had any IPF patient who was taking fluvoxamine? A. No, I have not.") (Morrow); Tr. 492:23-25 ("Q. Doctor, have you ever prescribed Pirfenidone to a patient who's taking fluvoxamine? A. No, never.") (Duncan)).

Plaintiffs also present arguments about fluvoxamine's multiple indications – from treatment of obsessive-compulsive disorder, anxiety, and depression to its potential as a treatment for COVID-19 – as further "evidence that the Proposed Label would induce infringement." (D.I. 374 at 11-12). I do not find this evidence persuasive. Plaintiffs have provided no evidence suggesting fluvoxamine's indications for the treatment of anxiety and depression in addition to OCD are new indications. Therefore, this information does nothing to lessen the persuasive impact of Plaintiffs' inability to cite a single example of a patient being prescribed both pirfenidone and fluvoxamine in the seven years both drugs have been approved and on the market.

As for Plaintiffs' argument about fluvoxamine's "potential" as a treatment for COVID-19, Plaintiffs acknowledge fluvoxamine has not been approved for the treatment of COVID-19 and

Plaintiffs' expert, Dr. Nathan, admitted that although he has treated patients suffering from COVID-19, he personally has never prescribed fluvoxamine for the treatment of COVID-19. (Tr. 263:11-264:15). Plaintiffs' evidence relating to the use of fluvoxamine for the treatment of COVID-19 essentially boils down to Dr. Nathan's personal speculation. Fluvoxamine "might find its place into various cocktails of therapies with monoclonals, remdesivir, and other drugs," and, "I think there's probably increasing uptake or use of fluvoxamine for patients with COVID." (Tr. 264:2-4, 14-15). I find this is insufficient evidence of a meaningful increase in the likelihood that a patient in need of pirfenidone therapy will also be prescribed fluvoxamine.

Moreover, even if it were more likely than not that there would be a patient who is prescribed both pirfenidone and fluvoxamine, Plaintiffs have not proven that infringement of the Asserted Claims would likely ensue. I find Dr. Morrow's testimony that a physician presented with such a situation would likely choose a non-infringing treatment adjustment over any of the claimed methods to be credible and persuasive. Dr. Morrow testified that, in light of the proposed label's clear warnings about drug-drug interactions between pirfenidone and fluvoxamine, a physician "would likely see [the warning in Section 7.1 about strong CYP1A2 inhibitors] and move to not co-prescribe the medications and choose something other than Pirfenidone. In this case, nintedanib." (Tr. 335:15-336:15); *see Takeda Pharms. U.S.A., Inc. v. West-Ward Pharm. Corp.*, 785 F.3d 625, 635 (Fed. Cir. 2015) (finding district court did not err in finding no direct infringement based on "insufficient evidence [the infringing] method would actually be practiced" where infringement depended on concomitant administration of two drugs and physician expert testified "they try to and can easily avoid concomitant administration of the drugs.").

Plaintiffs' argument regarding "the significance of the pirfenidone labeling history" does not help them. Plaintiffs argue that the FDA would not have insisted InterMune change its label

from contra-indicating co-administration of fluvoxamine and pirfenidone to including instructions allowing the co-administration of both drugs "if FDA did not expect there to be any patients for whom that reduction would be required." (D.I. 383 at 8). Even if the "expectations of the FDA" were relevant to answering the discrete factual question at issue here, without any testimony from any regulatory experts or anyone else with knowledge of the FDA's position and the basis for it, Plaintiffs' speculation about the "expectations" of the FDA is exactly that: speculation.

Because Plaintiffs have not provided sufficient evidence to show that, more likely than not, direct infringement of the Asserted Claims of the DDI patents will occur, Plaintiffs have not met their burden of proving infringement with respect to the DDI patents.

2. Invalidity

The Asserted Claims of the DDI patents disclose a method for administering pirfenidone to IPF patients also taking fluvoxamine by either discontinuing fluvoxamine prior to administration of pirfenidone (claim 6 of the '383 patent) or reducing the pirfenidone dose to allow concurrent administration of fluvoxamine and pirfenidone (claims 3 and 9 of the '002 patent). The parties agree the relevant priority date for the DDI patents is December 4, 2009. (D.I. 331-1 ¶¶ 99, 103, 109, 114).

Sandoz argues, "Each of these claims is invalid for obviousness under 35 U.S.C. § 103 in view of the combination of the Pirespa Label, 2008 Pirfenidone Report, the Luvox [fluvoxamine] Label, and either the '644 Publication or the FDA DDI Guidance." (D.I. 376 at 16). Specifically, Sandoz argues: (1) a POSA would have expected a drug-drug interaction between pirfenidone and fluvoxamine, (2) "Because a POSA would have expected a clinically significant drug-drug interaction between pirfenidone and fluvoxamine, any POSA who wanted to administer pirfenidone to an IPF patient who was also receiving fluvoxamine would have employed standard

strategies for avoiding drug-drug interactions," and (3) "Routine testing, as recommended by the FDA, would have confirmed the drug[-]drug interaction between pirfenidone and fluvoxamine." (*Id.* at 16-28).

I find that Sandoz has not proven, by clear and convincing evidence, that a POSA would have expected to find a significant drug-drug interaction between pirfenidone and fluvoxamine. Because I do not find the evidence shows that a POSA would have been concerned about drug-drug interactions between fluvoxamine and pirfenidone or that Plaintiffs' discovery of significant drug-drug interactions between the drugs was an "expected result," I do not reach Sandoz's two additional obviousness arguments, which are predicated on such a finding. *See Forest Lab'ys, LLC v. Sigmapharm Lab'ys, LLC*, 918 F.3d 928, 935 (Fed. Cir. 2019) ("where a problem was not known in the art, the solution to that problem may not be obvious, because ordinary artisans would not have thought to try at all because they would not have recognized the problem") (cleaned up); *Novartis Pharm. Corp. v. Watson Lab'ys, Inc.*, 611 F. App'x 988, 995 (Fed. Cir. 2015) ("Even an obvious solution, however, does not render an invention obvious if the problem solved was previously unknown.").

Sandoz argues that a POSA would have known the five enzymes responsible for metabolizing pirfenidone from the disclosures accompanying the Japanese approval of Pirespa (JTX0029; JTX0030) and would have known from the Luvox Label (JTX0033) that fluvoxamine inhibited metabolism by four of those five enzymes. (D.I. 376 at 16). The Luvox Label warns about "Potential Interactions with Drugs that Inhibit or are Metabolized by Cytochrome P450 Isoenzymes." (JTX0033 at 14). The Luvox Label states, "[I]t appears that fluvoxamine inhibits several cytochrome P450 enzymes that are known to be involved in the metabolism of other drugs

such as: [CYP1A2, 2C9, 3A4, and 2C19]," and, "*In vitro* data suggest that fluvoxamine is a relatively weak inhibitor of CYP2D6." (*Id.*).

While the Pirespa Label disclosed the five CYP enzymes (CYP1A2, 2C9, 2C19, 2D6, and 2E1) responsible for the metabolism of pirfenidone, prior to Plaintiffs' discovery, it was not known which of these enzymes, if any, was primarily responsible for pirfenidone's metabolism. (Tr. 117:18-22). That "Pirfenidone is primarily metabolized by CYP1A2" was a novel discovery by InterMune and was not known prior to the DDI patents' priority date. (*Id.*). What was believed at the time about pirfenidone's potential for drug-drug interactions is reflected in the Pirespa Label: "It is estimated that [pirfenidone] is insusceptible to CYP inhibition by other drugs since multiple CYP molecules are involved in metabolism reaction." (JTX0029 at 8). The 2008 Pirfenidone Report also taught that pirfenidone was not susceptible to drug-drug interactions. "Pirfenidone is unlikely to have pharmacokinetic interactions with other drugs," because, in part, "Pirfenidone is metabolized not by a particular CYP isoform but by multiple isoforms (CYP1A2, 2C9, 2C19, 2D6, and 2E1) and is therefore unlikely to be affected by CYP inhibition by concomitant drugs. . . ." (JTX0030 at 43).

I find that the language in the Pirespa Label and the 2008 Pirfenidone Report expressly teaching pirfenidone is not susceptible to CYP inhibition by concomitant drugs belies Sandoz's argument, "Given the substantial overlap of the enzymes that metabolized pirfenidone and the enzymes inhibited by fluvoxamine, a doctor would have reasonably expected to need to either avoid the co-administration of the two drugs or reduce the dose of pirfenidone if ever confronted with an IPF patient taking fluvoxamine." (D.I. 376 at 17). Although Sandoz is correct that the Luvox Label taught that fluvoxamine inhibits four of the five enzymes involved in the metabolism of pirfenidone, practically speaking, the Luvox Label taught inhibition of closer to three of the five

enzymes, as the Label expressly states, "*In vitro* data suggest" it is only "a relatively weak inhibitor" of one of those four enzymes. (JTX0033 at 14). I also find that the evidence at trial showed the general medical consensus regarding drug-drug interactions at the relevant time was that, for drugs metabolized by multiple enzymes, "Drug interactions are an exception." (Tr. 717:12-718:1) (Levy) (testifying that upon reviewing the 2008 Pirfenidone Report, "a POSA would consider that [pirfenidone] is like hundreds of drugs that are metabolized by multiple enzymes, and they are not susceptible to drug interactions. That's the baseline of drugs.").

Sandoz argues a POSA would have been especially concerned about drug-drug interactions involving pirfenidone because pirfenidone was known to have a narrow therapeutic window. (D.I. 376 at 19-20). The Luvox Label warned, "A clinically significant fluvoxamine interaction is possible with drugs having a narrow therapeutic ratio. . . ." (JTX0033 at 15). The U.S. Department of Health and Human Services' 2006 "Guidance for Industry" regarding drug interactions also warned, "Observed changes arising from metabolic drug-drug interactions" including "increased exposure to a toxic parent compound . . . can alter the safety and efficacy profile of a drug. . . ," and such an effect "is most obvious and expected for a drug with a narrow therapeutic range (NTR), but is also possible for non-NTR drugs as well . . . ." (JTX0032 at 5-6). These warnings do show that a POSA would have had more reason to be concerned about the clinical implications of a drug-drug interaction involving a drug with a narrow therapeutic window like pirfenidone. (Tr. 395:15-20 (Ortiz de Montellano) ("A narrow window therapeutic agent has only a small range of concentrations where it is effective but not toxic. And the reason this is important, of course, is that in a drug-drug interaction, a small increase in the concentration, in a narrow therapeutic window drug, can toss it into toxicity.")). Such a showing, however, is not sufficient to overcome

the fact that the prior art affirmatively taught that pirfenidone was unlikely to be susceptible to drug-drug interactions in the first place.

In view of (1) the express teachings-away of the Pirespa Label and the 2008 Pirfenidone Report, (2) the fact that fluvoxamine was known to inhibit only between three and four of the five enzymes responsible for the metabolism of pirfenidone, (3) the lack of an understanding at the time that any one of the five identified CYP enzymes was primarily responsible for the metabolism of pirfenidone, and (4) the general understanding at the time that drug-drug interactions involving drugs metabolized via multiple enzymes were the exception rather than the expectation, I find that Sandoz has not proven by clear and convincing evidence that a POSA would have expected to find a drug-drug interaction between pirfenidone and fluvoxamine. Therefore, I find Sandoz has not met its burden in proving the DDI patents were obvious.

IV. CONCLUSION

For the reasons stated above, I find that Plaintiffs have not proven their claim of induced infringement of the Asserted Claims. I further find Sandoz proved the Asserted Claims of the LFT patents are invalid as obvious but did not prove the Asserted Claims of the DDI patents are invalid as obvious.

The parties should meet and confer about how to proceed from this point. The parties are asked to submit a joint status report within one week, preferably with a jointly proposed final judgment.